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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/043,418	01/10/2002	Cynthia A. Henson	960296.97486	9063

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EXAMINER	
RAO, MANJUNATH N	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 11/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/043,418	HENSON ET AL.	
	Examin r	Art Unit	
	Manjunath N. Rao, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with th correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 August 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9* is/are pending in the application.

4a) Of the above claim(s) *2-5,8 and 9* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,6 and 7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 January 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *2-25-02* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-9 are currently pending and are present for examination. Claims 1, 6-7 are now under consideration. Claims 2-5, 8-9 remain withdrawn from consideration as being drawn to non-elected invention.

Election/Restrictions

Applicant's election with traverse of Group I, drawn to modified α-glucosidase enzyme in Paper filed on 8-18-03 is acknowledged. The traversal is on the ground(s) that coexamination of all of Groups drawn to modified α-glucosidase is unnecessary as no separate searches are required. This is not found persuasive because while the searches for the modified α-glucosidase may appear to overlap, they are not coextensive. Furthermore, the searches will involve extensive search of the non-patent literature. However, in view of the claim amendments submitted by the applicant, Examiner has rejoined claim 7 to group I. The search for Groups II and III would each require the search of subclasses unnecessary for the search of elected Group I. The requirement is still deemed proper and is therefore made FINAL.

Claims 2-5, 8-9 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed in Paper filed on 8-13-03.

Priority

Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged.

Drawings

Drawings submitted in this application are accepted by the Examiner for examination purposes only.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 6 and 7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 1, 6 and 7 are drawn to a modified barley α-glucosidase with specific mutations at specific amino acid positions. However, applicants do not provide a SEQ ID NO for the parent α-glucosidase because of which it is impossible for the Examiner to perform a search in order to determine the specific mutations at said positions rendering the claims unclear or indefinite. Examiner urges applicants to provide the SEQ ID NO for the parent α-glucosidase that has been modified.

Claim 7 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 7 recites the phrase, for example, "removing an aspartate *from* residue 105". It is not clear to the Examiner as to how an aspartate can be removed from a residue. It appears that applicants meant to recite "deletion of the aspartate at position 105". If this is so amending the above phrase and such similar phrases in claim 7 would overcome the above rejection.

Claim 7 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 7 recites the limitation "removing an aspartate" (i.e., deletion of an aspartate) in lines 4, 6, 12. There is insufficient antecedent basis for this limitation in the claim. Claim 7 depends from claim 6 which is exclusively drawn to a modified enzyme wherein the modifications are "substitutions" and not "deletions".

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 6 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a modified barley α-glucosidase (SEQ ID NO:1) which retains the activity at a higher temperature than wild type enzyme, wherein the modification is substitution of the amino acid at positions 101, 340, 372 and 694, does not reasonably provide enablement for any modified α-glucosidase comprising a substitution of any amino acid in SEQ ID NO:1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the

prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claim 6 is so broad as to encompass any modified α-glucosidase from any or all sources including recombinants having activity at higher temperature than their corresponding wild type enzyme. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of α-glucosidases broadly encompassed by the claim. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the nucleotide mutant with amino acid substitutions in SEQ ID NO:1 listed above. It would require undue experimentation of the skilled artisan to make and use the claimed polypeptides. The specification is limited to teaching the substitutions at positions 101, 340, 372 and 694 in SEQ ID NO:1 only, but provides no guidance with regard to the making of variants and mutants comprising substitution of any amino acid residue in SEQ ID NO:1 or with regard to other uses. In view of the great breadth of the claim, amount of experimentation required to make the claimed polypeptides, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), the claimed invention would require undue

experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polypeptides encompassed by this claim.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of SEQ ID NOS:1 because the specification does not establish: (A) regions of the protein structure which may be modified (by substitution only) without affecting α-glucosidase activity; (B) the general tolerance of α-glucosidase to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying (i.e., substitution of) any amino acid residue with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including variants of SEQ ID NO:1 with an enormous number of amino acid modifications (i.e., substitutions). The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)).

Without sufficient guidance, determination of variants of SEQ ID NO:1 having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim 6 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 6 is directed to polypeptide variants of SEQ ID NO:1. Claim 6 is rejected under this section of 35 USC 112 because the claim is directed to a genus of polypeptides derived from SEQ ID NO:1 including modified polypeptide sequences, modified by at least one substitution of an amino acid residue in SEQ ID NO:1 that have not been disclosed in the specification. No description has been provided of the modified polypeptide sequences encompassed by the claim. No information, beyond the characterization of substitutions at only 4 positions (i.e., 101, 340, 372, and 694) in a amino acid sequence that is 877 amino acids is length has been provided by applicants which would indicate that they had possession of the claimed genus of modified polypeptides. The specification does not contain any disclosure of the structure of all the polypeptide sequences derived from SEQ ID NO:1 by amino acid substitutions, including fragments and variants within the scope of the claimed genus. The genus of polypeptides claimed is a large variable genus including peptides which can have a wide variety of structures. Therefore many structurally unrelated polypeptides are encompassed within the scope of these

claims. The specification discloses only 4 species of the claimed genus which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 7 is rejected under 35 U.S.C. 102(a) as being anticipated by Frandsen et al. (Plant Physiol., 2000, Vol. 123:275-282). This rejection is based upon the public availability of a printed publication. Claim 7 of the instant application is drawn to a modified α-glucosidase, wherein the modified form differs from wild-type barley α-glucosidase by at least one substitution or deletion, such that the modified enzyme retains enzymatic activity at a higher temperature than wild type enzyme, wherein the deletion is selected from a group consisting of for example removing aspartate at position 105, position 508 or position 764. Frandsen et al. disclose such a modified α-glucosidase wherein at least the aspartates at positions 105, 508 and

764 have been removed. The enzyme disclosed by Frandsen et al. does not have aspartate at positions 105, 508 or 764. The reference does not explicitly disclose that the enzyme retains activity at a higher temperature than the wild type enzyme that applicants are referring to. However, since the modifications are exactly the same as claimed, Examiner takes the position that the enzyme inherently has thermostability and is capable of retaining its activity at a higher temperature than the wild type that applicants are referring to. Thus Frandsen et al. anticipate claim 7 of this application as written.

Since the Office does not have the facilities for examining and comparing applicants' protein with the protein of the prior art (for thermostable characteristic), the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not possess the same material structural and functional characteristics of the claimed protein). See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald* et al., 205 USPQ 594.

Claim 6 is rejected under 35 U.S.C. 102(b) as being anticipated by Nakao et al. (Eur. J. Biochem., 1994, Vol. 220(2):293-300). This rejection is based upon the public availability of a printed publication. Claim 6 of the instant application is drawn to a modified α-glucosidase , wherein the modified form differs from wild-type barley α-glucosidase by at least one substitution, such that the modified enzyme retains enzymatic activity at a higher temperature than wild type enzyme. Nakao et al. disclose such a modified α-glucosidase wherein at least one amino acid in the wild type barley α-glucosidase has been substituted and wherein the modified enzyme retains the activity at a higher temperature compared to the wild type barley enzyme.

Since there is no limitation placed on the number of substitutions that can be present in the barley α-glucosidase amino acid sequence, claim 6 reads on the enzyme disclosed by Nakao et al. Thus Nakao et al. anticipate claims 6 of this application as written.

Claim 6 is rejected under 35 U.S.C. 102(b) as being anticipated by Nakao et al. (Eur. J. Biochem., 1994, Vol. 220(2):293-300). This rejection is based upon the public availability of a printed publication. Claim 6 of the instant application is drawn to a modified α-glucosidase , wherein the modified form differs from wild-type barley α-glucosidase by at least one substitution, such that the modified enzyme retains enzymatic activity at a higher temperature than wild type enzyme. Nakao et al. disclose such a modified α-glucosidase wherein at least one amino acid in the wild type barley α-glucosidase has been substituted and wherein the modified enzyme retains the activity at a higher temperature compared to the wild type barley enzyme. Since there is no limitation placed on the number of substitutions that can be present in the barley α-glucosidase amino acid sequence, claim 6 reads on the enzyme disclosed by Nakao et al. Thus Nakao et al. anticipate claims 6 of this application as written.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Skadsen et al. (US 5,763,252 6-9-1998), Scandurra et al. (Biochimie, 1998, Vol. 80(11) :933-941), Li et al. (Protein Engg., 1997, Vol. 10(10) :1199-1204), and Igarashi et al. (Biosci. Biotechnol. Biochem., 1999, Vol. 63(9):1535-1540). Claims 1, 6-7 in this instant application are drawn to modified α -glucosidases of barley wherein some specific amino acids are replaced with prolines or some specific amino acids are deleted such that the resulting mutant retains activity at a higher temperature than the wild type enzyme.

Skadsen et al. teach the cDNA encoding the barley α-glucosidase. The reference also teaches its use in fermentative processes. The reference also teaches that those skilled in the art would know to make mutants of the same. However, the reference does not teach any specific mutants which are thermostable.

Scandurra et al. teaches extensively the thermostable nature of some proteins and explores the reasons for such thermostability. The reference compares the protein structure of mesophilic proteins with that of thermophilic proteins and concludes that in general, thermophilic proteins have strategic placements of prolines in ß turns that render said proteins to be more stable and thermostable. The reference does not however teach this with reference to α-glucosidase of barley.

Based on studies such as that of Scandurra et al. Li et al. and Igarashi et al. perform proline substitutions and successfully arrive at mutants of glucosidases that are thermostable. Li et al. teach proline substitutions in glucoamylase of *Aspergillus* sp. and Igarashi et al. teach the engineering of a bacterial thermostable mutant of another glucosidase.

Combining the teachings of all the above references, it would have been obvious to those skilled in the art to take the cDNA and the encoded amino acid sequence of barley α-glucosidase taught by Skadsen et al. and use it to make thermostable mutants or variants of the same using the teachings of Scandurra et al. and examples of Li et al. and Igarashi et al. by strategic placements of prolines in place of selected amino acids and arrive at the same invention as claimed in claims 1, 7. One of ordinary skill in the art would have been motivated to do so due to the commercial demand for α-glucosidase in the fermentation industry. One of ordinary skill in the art would have a reasonable expectation of success since Skadsen et al. provide the complete cDNA cline and the amino acid sequence of barley α-glucosidase and increasing the thermostability of enzymes by proline substitution appears to be well known in the art as taught by the above references along with some successful mutants made from fungal and bacterial sources. While identifying strategic amino acids positions for proline substitutions would require some experimentation, such experimentation would be well within the knowledge of those skilled in the art.

Therefore the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art.

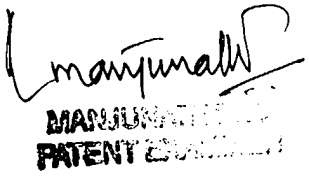
This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Conclusion

None of the claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Manjunath Rao whose telephone number is (703) 306-5681. The Examiner can normally be reached on M-F from 7:30 a.m. to 4:00 p.m. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, P.Achutamurthy, can be reached on (703) 308-3804. The fax number for Official Papers to Technology Center 1600 is (703) 305-3014. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.



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10/29/03